

~~when Y is NR_6 , then $k = 2-4$;~~

~~when Y is O and M or W is O , then $k = 1-4$~~

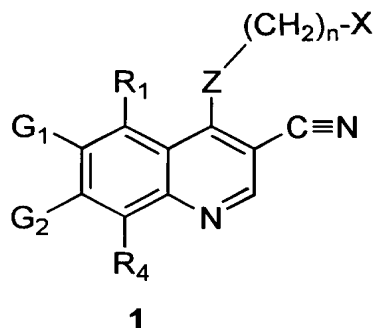
~~when W is not a bond with Het bonded through a nitrogen atom, then $q = 2-4$~~

~~and when W is a bond with Het bonded through a nitrogen atom and Y is O or NR_6 , then $k = 2-4$, G_1 , G_2 , R_1 , R_4 , Z , n , and X are defined in the specification or a pharmaceutically acceptable salt thereof~~ which are useful as antineoplastic agents and in the treatment of polycystic kidney disease.

In the Claims

Claim 1 has been amended as follows:

1. A compound of Formula 1 having the structure:



wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy,

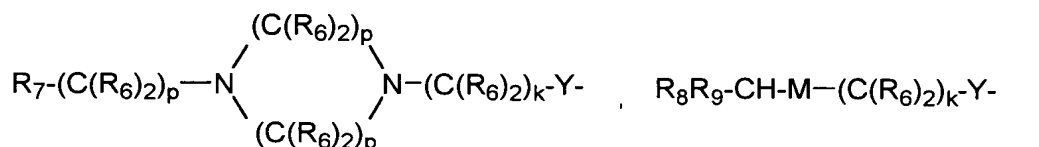
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benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, methylmercapto, and benzoylamino;

Z is -NH-, -O-, -S-, or -NR- ;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

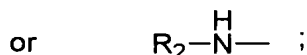
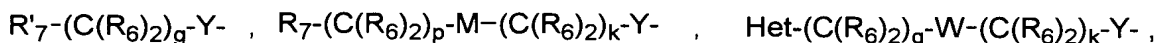
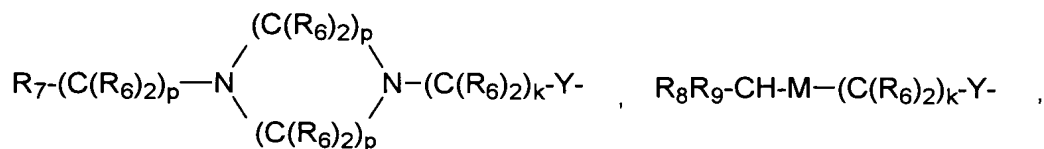
G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,



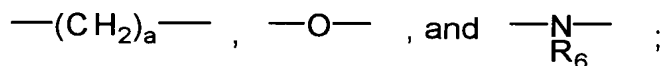
$R_7-(C(R_6)_2)_g-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_k-Y-$

with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group

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Y is a divalent radical selected from the group consisting of



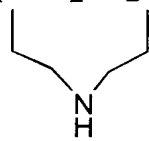
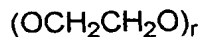
R₇ is -NR₆R₆, -J, -OR₆, -N(R₆)₃⁺, or -NR₆(OR₆);

R'₇ is -NR₆(OR₆), -N(R₆)₃⁺, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

M is >NR₆, -O-, >N-(C(R₆)₂)_pNR₆R₆, or >N-(C(R₆)₂)_p-OR₆;

W is >NR₆, -O- or is a bond;

Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane,



1,3-dioxolane, tetrahydropyran, and ;

wherein the heterocycle is optionally mono- or di-substituted on carbon or nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy, -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the mono-valent radicals -

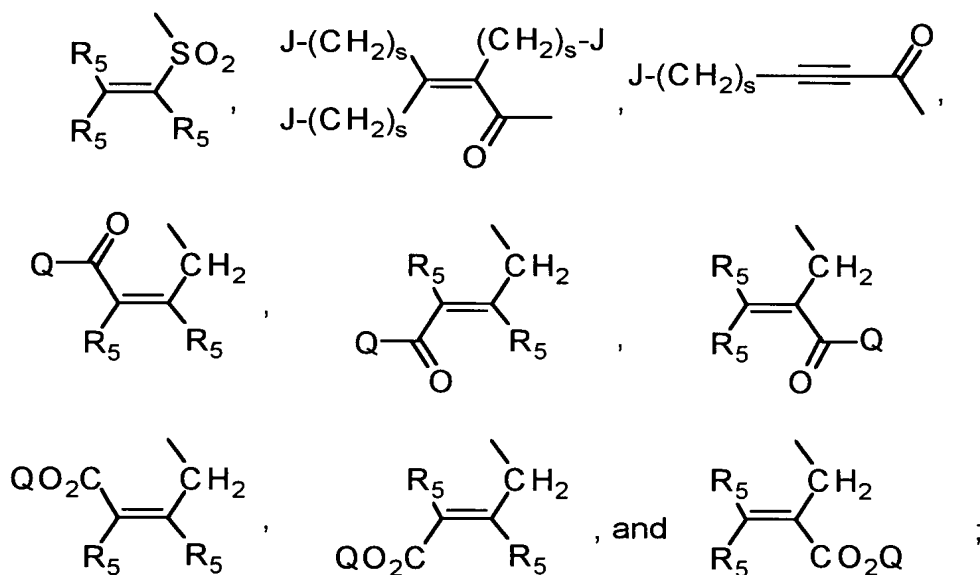
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$(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, or optionally mono or di-substituted on a saturated carbon with divalent radicals -O- or $-O(C(R_6)_2)_sO-$;

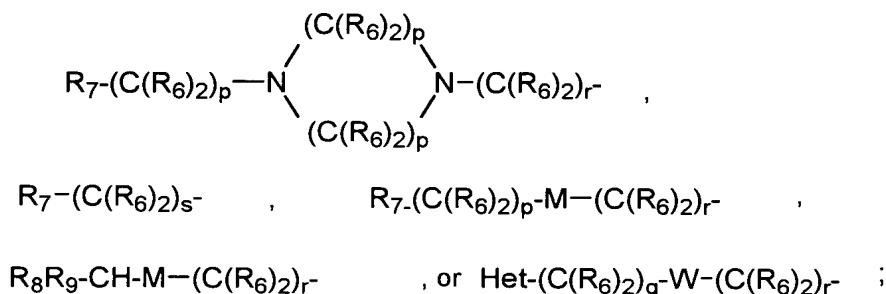
R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

R_2 , is selected from the group consisting of

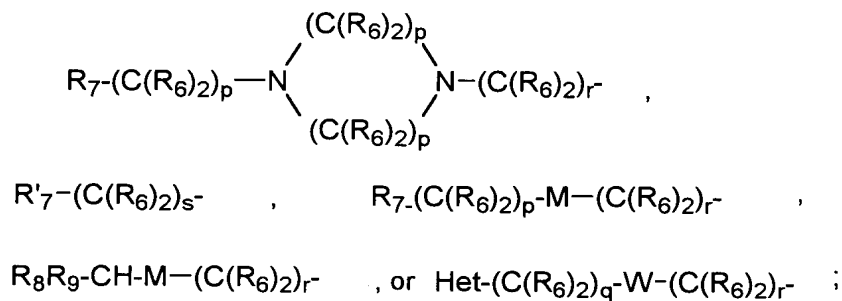
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



with the proviso that at least one of the R₃ groups is selected from the group



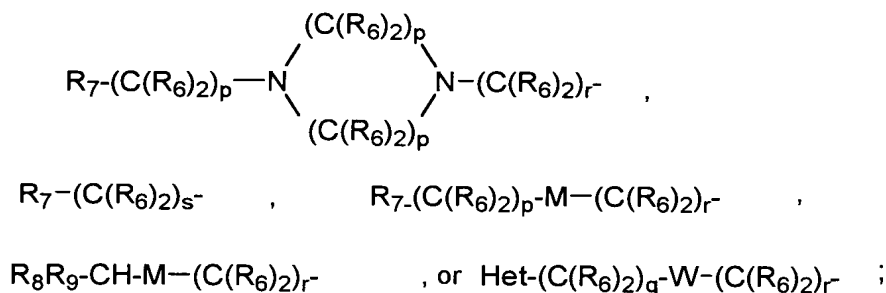
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with the proviso that for said at least one R₃ group the moiety

Het-(C(R₆)₂)_g-W-(C(R₆)₂)_r-

cannot be morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms, or azacycloalkyl-N-alkyl of 3-11 carbon atoms;

R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

a = 0 or 1;

g = 1-6;

k = 0-4;

n is 0-1;

p = 2-4;

q=0-4;

r = 1-4;

s = 1-6;

u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

or a pharmaceutically acceptable salt thereof,

provided that

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when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃⁺, or -NR₆(OR₆), then g = 2-6;

when M is -O- and R₇ is -OR₆, then p = 1-4;

when Y is -NR₆-, then k = 2-4;

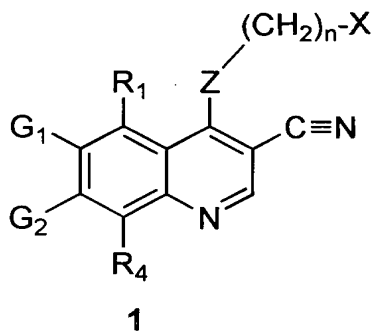
when Y is -O- and M or W is -O-, then k = 1-4

when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4

and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or -NR₆-, then k = 2-4.

Claim 6 has been amended to read as follows:

6. A method of treating, inhibiting the growth of, or eradicating a neoplasm in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms,

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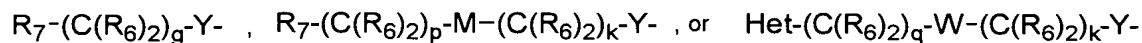
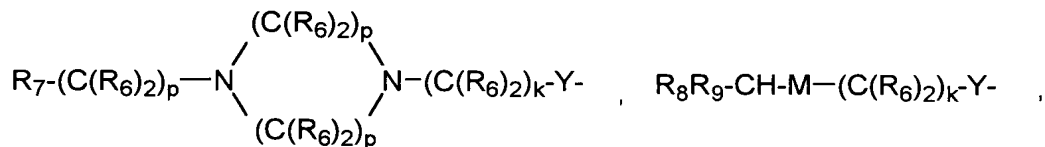
alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, methylmercapto, and benzoylamino;

Z is -NH-, -O-, -S-, or -NR- ;

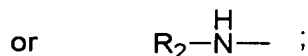
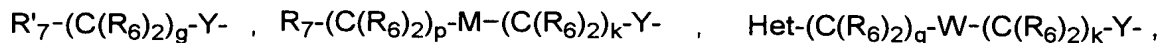
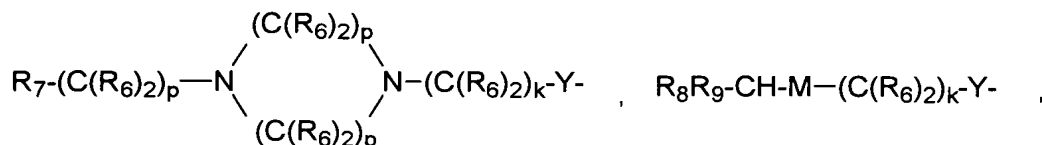
R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G1, G2, R1, and R4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

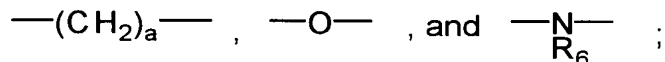
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with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group



Y is a divalent radical selected from the group consisting of



R₇ is -NR₆R₆, -J, -OR₆, -N(R₆)₃⁺, or -NR₆(OR₆);

R'₇ is -NR₆(OR₆), -N(R₆)₃⁺, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

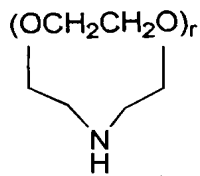
M is >NR₆, -O-, >N-(C(R₆)₂)_pNR₆R₆, or >N-(C(R₆)₂)_p-OR₆;

W is >NR₆, -O- or is a bond;

Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine,

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tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane,



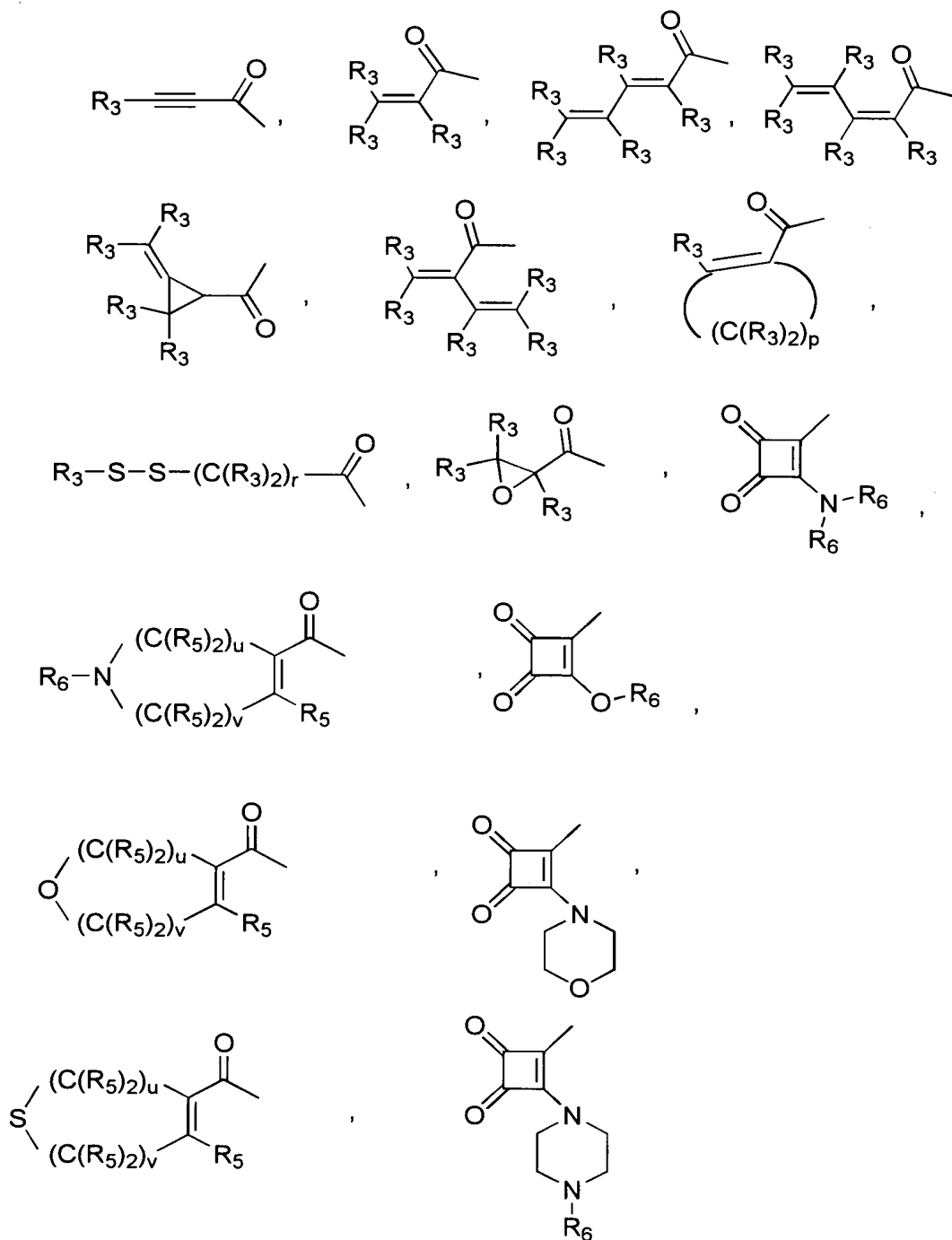
1,3-dioxolane, tetrahydropyran, and

wherein the heterocycle is optionally mono- or di-substituted on carbon or nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy, -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the mono-valent radicals -C(R₆)₂)_sOR₆ or -(C(R₆)₂)_sN(R₆)₂, or optionally mono or di-substituted on a saturated carbon with divalent radicals -O- or -O(C(R₆)₂)_sO-;

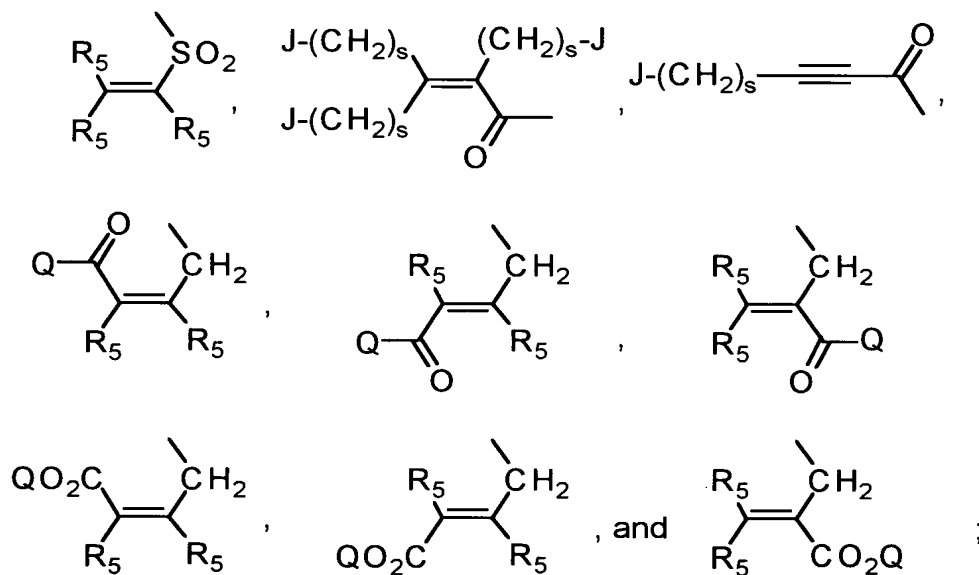
R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

R₂, is selected from the group consisting of

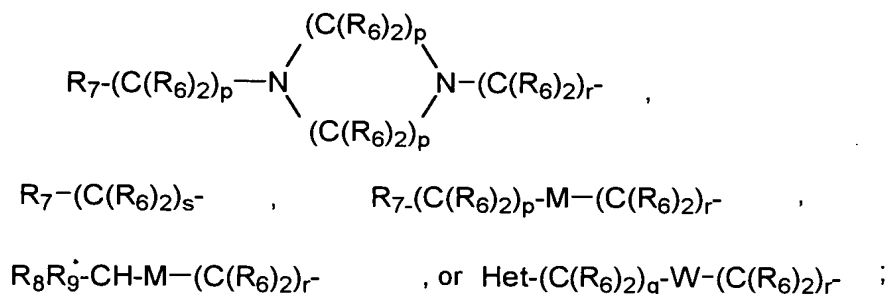
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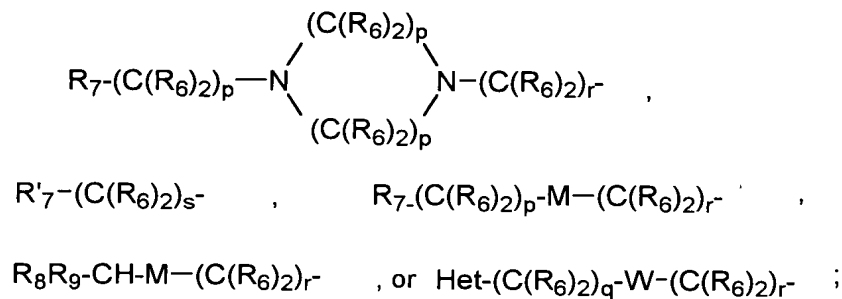
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



with the proviso that at least one of the R₃ groups is selected from the group



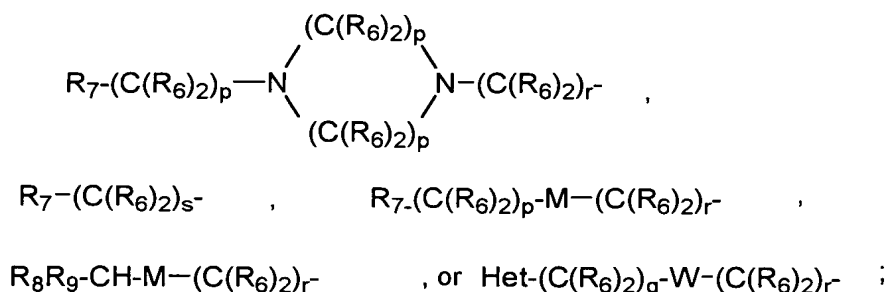
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with the proviso that for said at least one R_3 group the moiety

Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-

cannot be morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms, or azacycloalkyl-N-alkyl of 3-11 carbon atoms;

R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

a = 0 or 1;

g = 1-6;

k = 0-4;

n is 0-1;

p = 2-4;

q=0-4;

r = 1-4;

s = 1-6;

u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

or a pharmaceutically acceptable salt thereof,

provided that

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when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃⁺, or -NR₆(OR₆), then g = 2-6;

when M is -O- and R₇ is -OR₆, then p = 1-4;

when Y is -NR₆-, then k = 2-4;

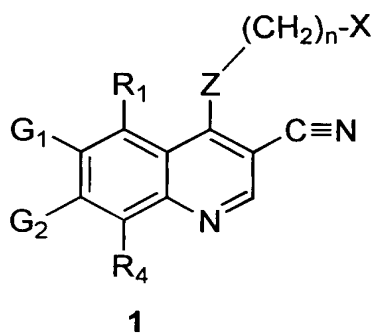
when Y is -O- and M or W is -O-, then k = 1-4

when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4

and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or -NR₆-, then k = 2-4.

7. The method according to claim 6 wherein the neoplasm is selected from the group consisting of breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, and lung.

8. A method of treating, inhibiting the progression of, or eradicating polycystic kidney disease in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-

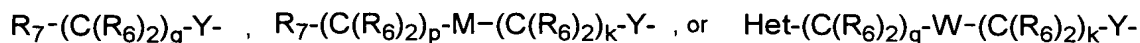
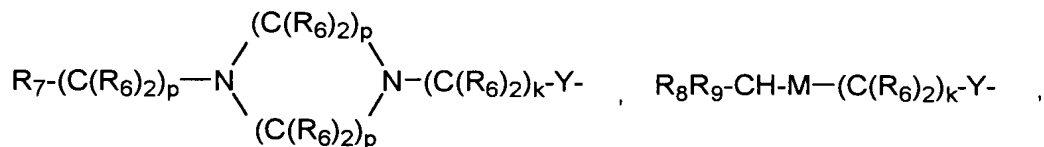
substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, methylmercapto, and benzoylamino;

Z is -NH-, -O-, -S-, or -NR- ;

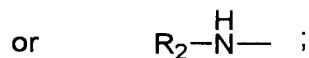
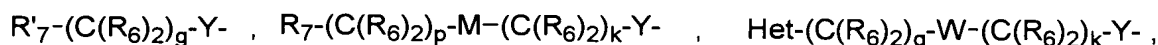
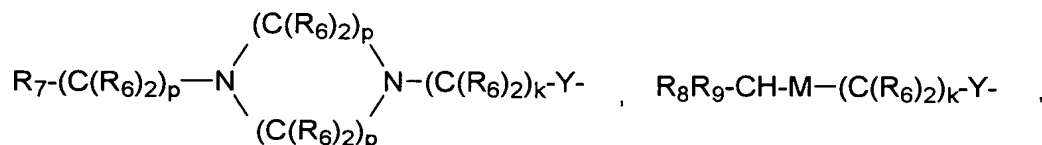
R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G1, G2, R1, and R4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphanyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

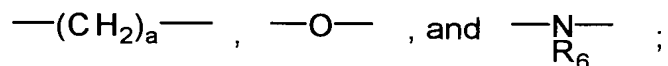
A



with the proviso that either G_1 or G_2 or both G_1 and G_2 must be a radical selected from the group



Y is a divalent radical selected from the group consisting of



R_7 is $-NR_6R_6$, $-J$, $-OR_6$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

R'_7 is $-NR_6(OR_6)$, $-N(R_6)_3^+$, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

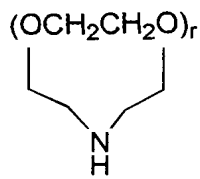
M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_pNR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$;

W is $>NR_6$, $-O-$ or is a bond;

Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine,

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tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane,



1,3-dioxolane, tetrahydropyran, and

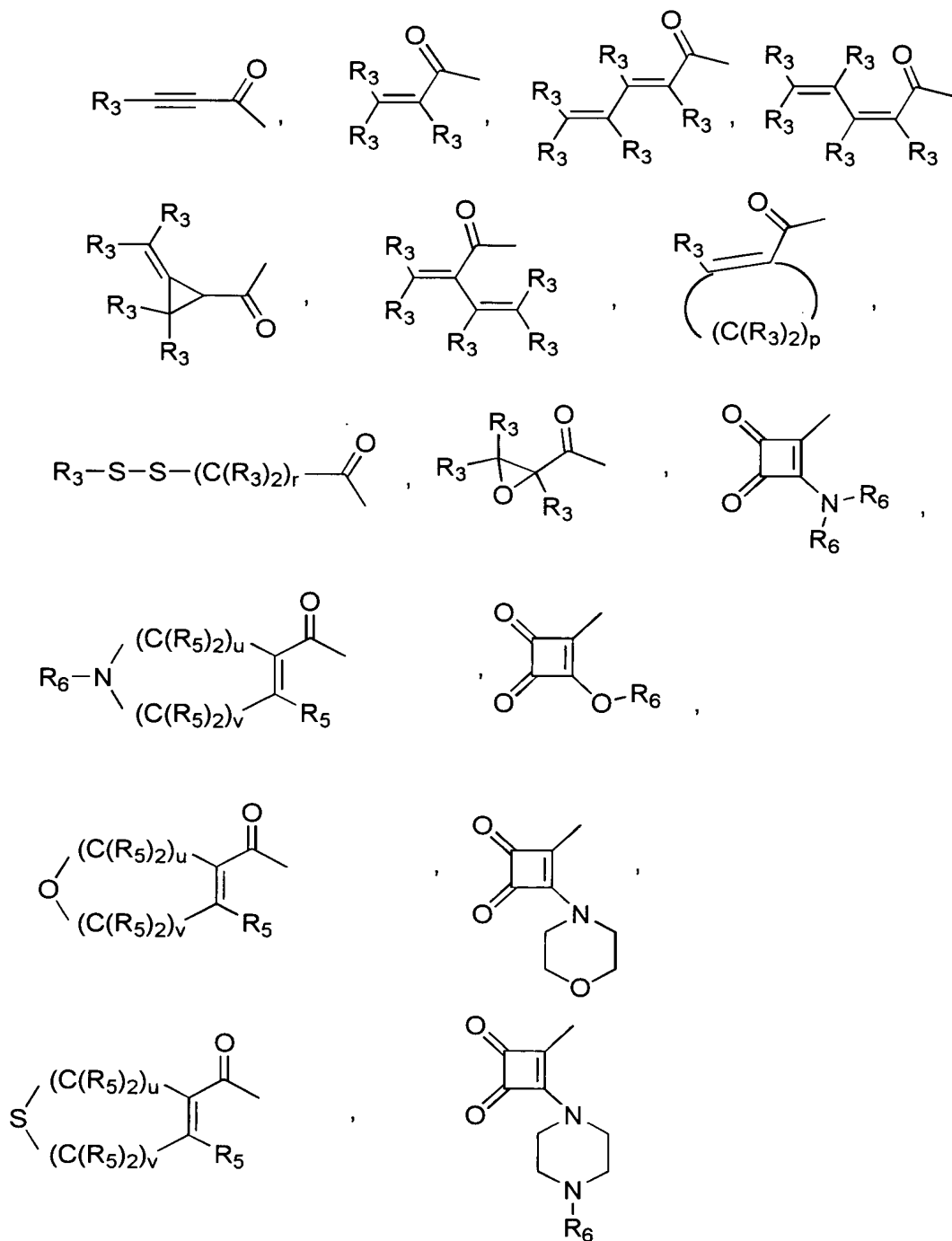
;

wherein the heterocycle is optionally mono- or di-substituted on carbon or nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with the mono-valent radicals $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, or optionally mono or di-substituted on a saturated carbon with divalent radicals $-O-$ or $-O(C(R_6)_2)_sO-$;

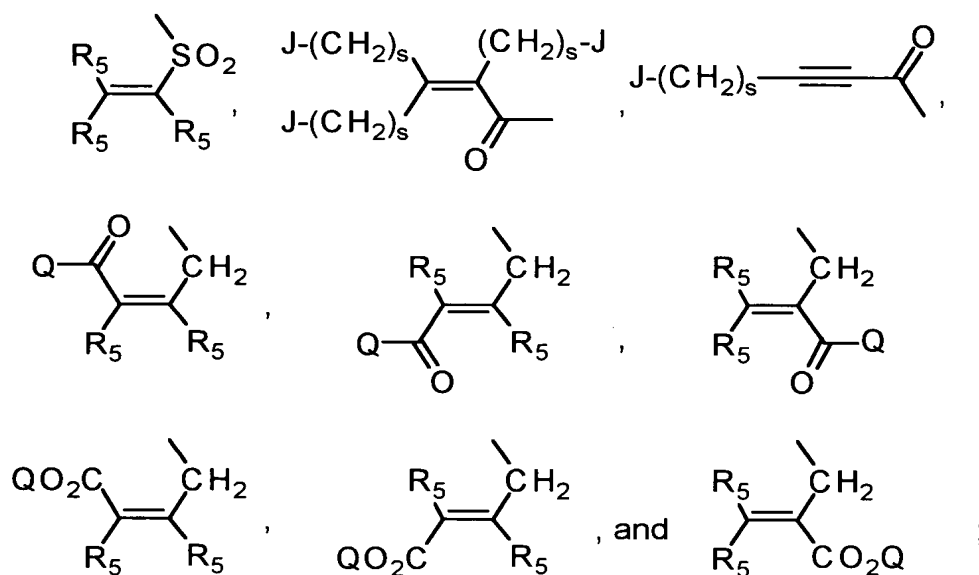
R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

R_2 , is selected from the group consisting of

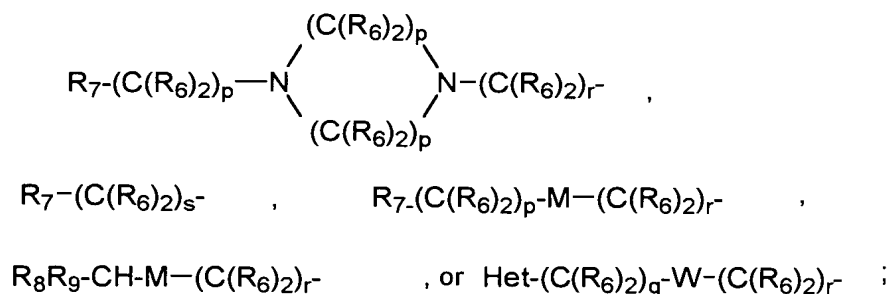




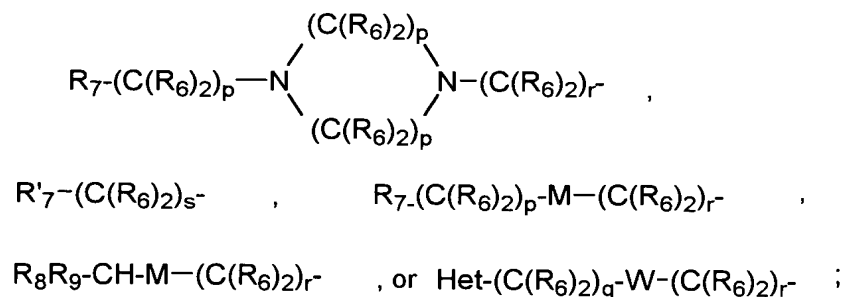
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



with the proviso that at least one of the R₃ groups is selected from the group



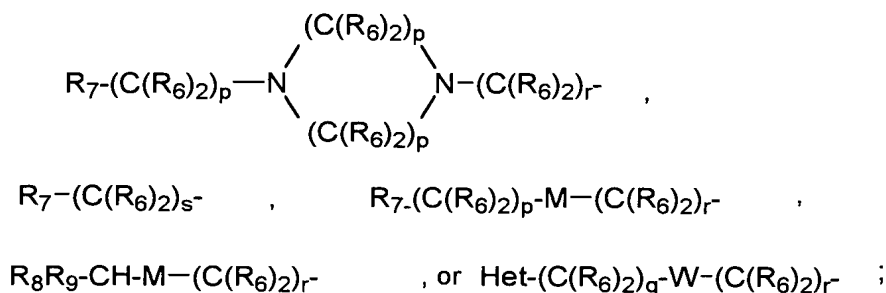
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with the proviso that for said at least one R_3 group the moiety

Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-

cannot be morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms, or azacycloalkyl-N-alkyl of 3-11 carbon atoms;

R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

a = 0 or 1;

g = 1-6;

k = 0-4;

n is 0-1;

p = 2-4;

q=0-4;

r = 1-4;

s = 1-6;

u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

or a pharmaceutically acceptable salt thereof,

provided that

when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃⁺, or -NR₆(OR₆), then g = 2-6;

when M is -O- and R₇ is -OR₆, then p = 1-4;

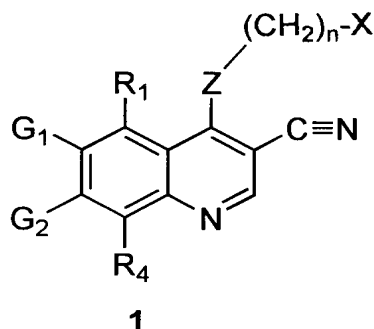
when Y is -NR₆-, then k = 2-4;

when Y is -O- and M or W is -O-, then k = 1-4

when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4

and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or -NR₆-, then k = 2-4.

9. A pharmaceutical composition which comprises a compound of formula 1 having the structure



wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono- di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12

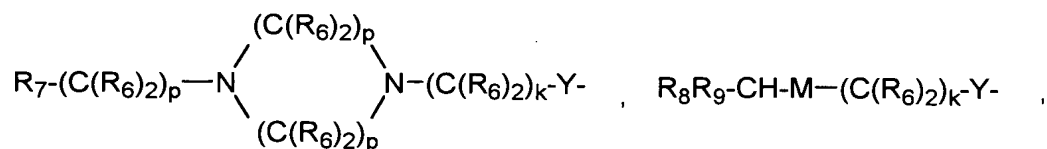
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carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, methylmercapto, and benzoylamino;

Z is -NH-, -O-, -S-, or -NR- ;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

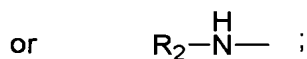
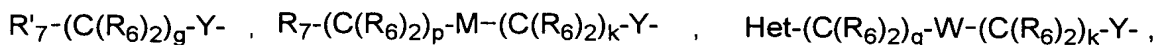
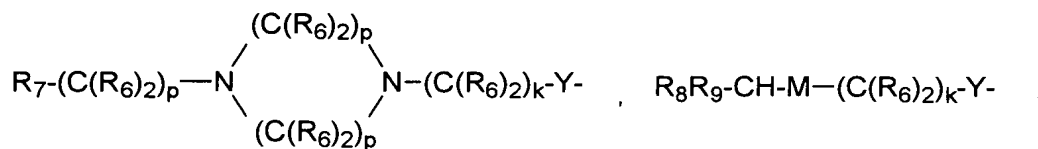
G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,



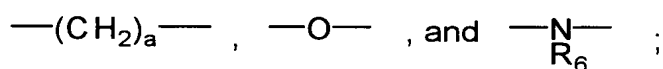
$\text{R}_7\text{-(C(R}_6\text{)}_2\text{)}_g\text{-Y-}$, $\text{R}_7\text{-(C(R}_6\text{)}_2\text{)}_p\text{-M-(C(R}_6\text{)}_2\text{)}_k\text{-Y-}$, or $\text{Het-(C(R}_6\text{)}_2\text{)}_q\text{-W-(C(R}_6\text{)}_2\text{)}_k\text{-Y-}$

with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group

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Y is a divalent radical selected from the group consisting of



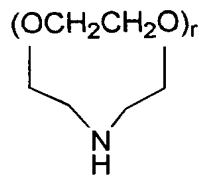
R₇ is -NR₆R₆, -J, -OR₆, -N(R₆)₃⁺, or -NR₆(OR₆);

R'₇ is -NR₆(OR₆), -N(R₆)₃⁺, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

M is >NR₆, -O-, >N-(C(R₆)₂)_pNR₆R₆, or >N-(C(R₆)₂)_p-OR₆;

W is >NR₆, -O- or is a bond;

Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane,



1,3-dioxolane, tetrahydropyran, and

wherein the heterocycle is optionally mono- or di-substituted on carbon or nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy, -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the mono-valent radicals -

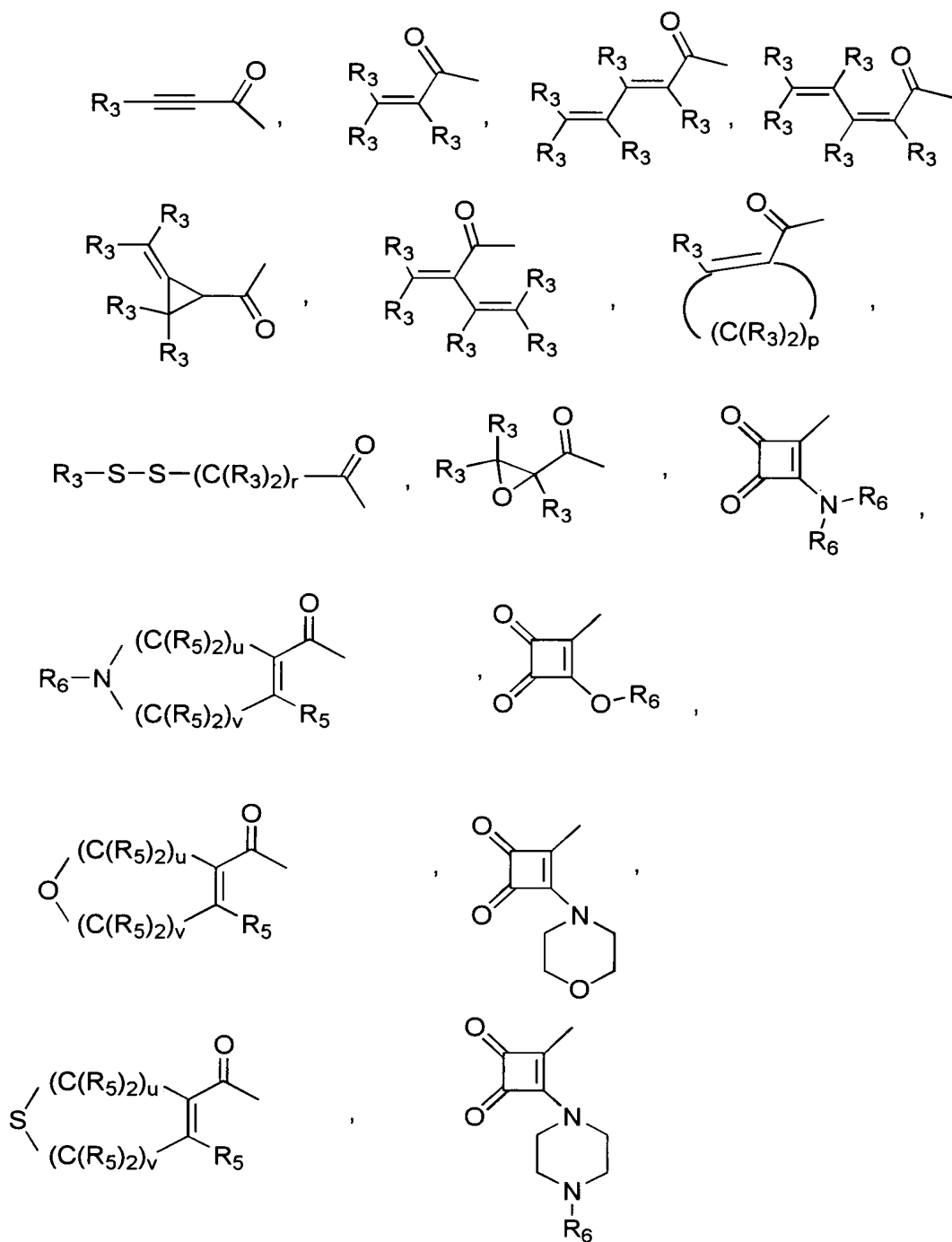
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$(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$, or optionally mono or di-substituted on a saturated carbon with divalent radicals -O- or $-O(C(R_6)_2)_sO-$;

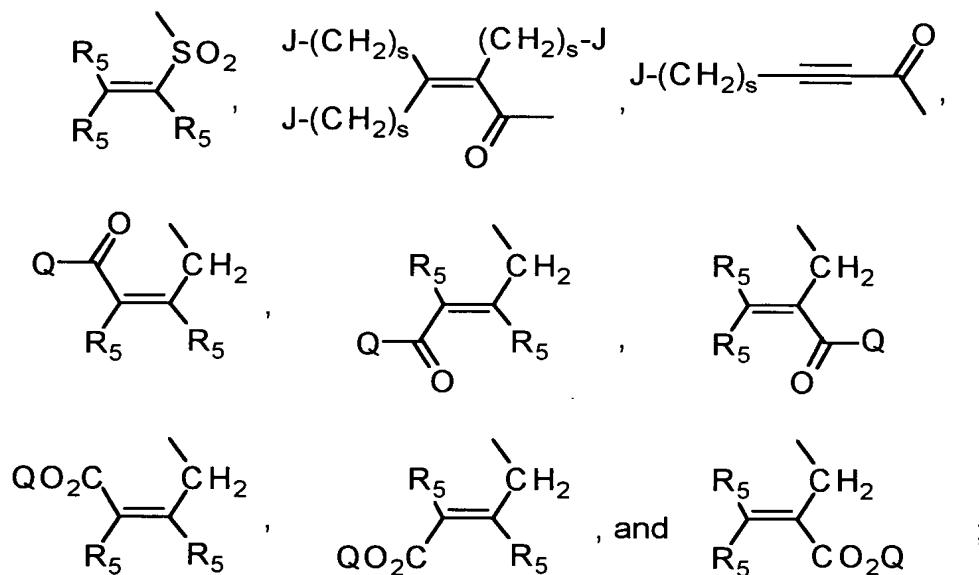
R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

R_2 , is selected from the group consisting of

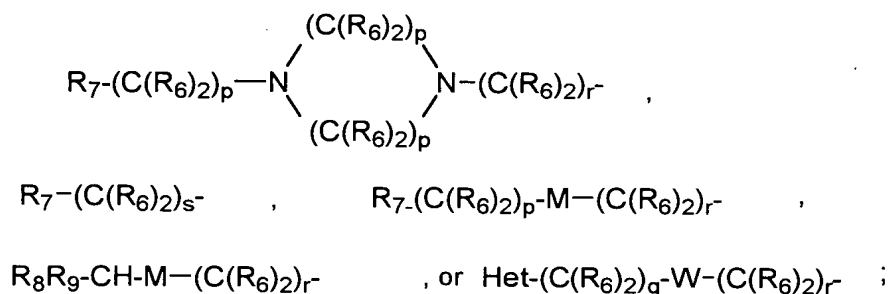
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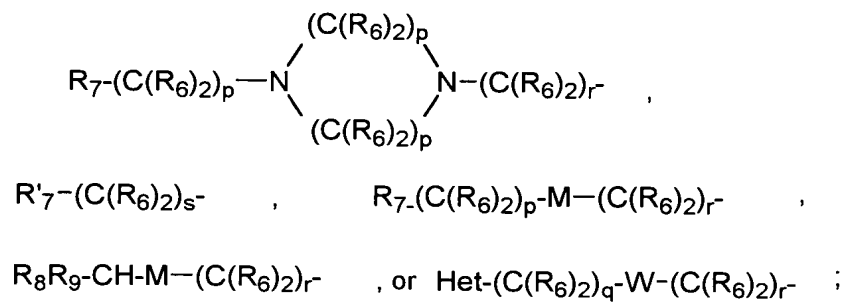
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



with the proviso that at least one of the R₃ groups is selected from the group



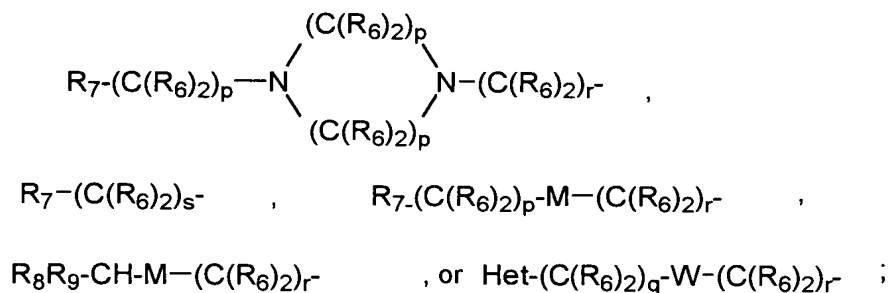
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with the proviso that for said at least one R_3 group the moiety

Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r-

cannot be morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms, or azacycloalkyl-N-alkyl of 3-11 carbon atoms;

R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

a = 0 or 1;

g = 1-6;

k = 0-4;

n is 0-1;

p = 2-4;

q=0-4;

r = 1-4;

s = 1-6;

u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

or a pharmaceutically acceptable salt thereof,

provided that

when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃⁺, or -NR₆(OR₆), then g = 2-6;

when M is -O- and R₇ is -OR₆, then p = 1-4;

when Y is -NR₆-, then k = 2-4;

when Y is -O- and M or W is -O-, then k = 1-4

when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4

and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or -NR₆-, then k = 2-4.